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Polypharmacy and health outcomes in atrial fibrillation: a systematic review and meta-analysis

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ABSTRACT

Objective To undertake a systematic review and meta-analysis examining the impact of polypharmacy on health outcomes in atrial fibrillation (AF).

Data sources PubMed and Embase databases were searched from inception until 31 July 2019. Studies including post hoc analyses of prospective randomised controlled trials or observational design that examined the impact of polypharmacy on clinically significant outcomes in AF including mortality, hospitalisations, stroke, bleeding, falls and quality of life were eligible for inclusion.

Results A total of six studies were identified from the systematic review, with three studies reporting on common outcomes and used for a meta-analysis. The total study population from the three studies was 33 602 and 37.2% were female. Moderate and severe polypharmacy, defined as 5–9 medicines and >9 medicines, was observed in 42.7% and 20.7% of patients respectively, and was associated with a significant increase in all-cause mortality (Hazard ratio [HR] 1.36, 95% CI 1.20 to 1.54, p<0.001; HR 1.84, 95% CI 1.40 to 2.41, p<0.001, respectively), major bleeding (HR 1.32, 95% CI 1.14 to 1.52, p<0.001; HR 1.68, 95% CI 1.35 to 2.09, p<0.001, respectively) and clinically relevant non-major bleeding (HR 1.12, 95% CI 1.03 to 1.22, p<0.01; HR 1.48, 95% CI 1.33 to 1.64, p<0.01, respectively). There was no statistically significant association between polypharmacy and stroke or systemic embolism or intracranial bleeding. Among other examined outcomes, polypharmacy was associated with cardiovascular death, hospitalisation, reduced quality of life and poorer physical function.

Conclusions Polypharmacy is highly prevalent in the AF population and is associated with numerous adverse outcomes.

PROSPERO registration number CRD42018105298.

Key questions

What is already known about this subject?

- Polypharmacy has been associated with numerous adverse outcomes in selected general populations, including mortality, falls, hospitalisations, reduced quality of life and economic burden.
- A synthesis of the literature examining health outcomes associated with polypharmacy in the atrial fibrillation (AF) population has not been undertaken.

What does this study add?

- Polypharmacy in patients with AF is independently associated with an increased risk of adverse outcomes including all-cause mortality, major bleeding, clinically relevant non-major bleeding, hospitalisations, reduced quality of life and poorer physical function.

How might this impact on clinical practice?

- Regular reconciliation and review of a patient's prescribed and non-prescribed medicines can help identify inappropriate polypharmacy and provide opportunities to minimise polypharmacy-associated harm.

INTRODUCTION

In many countries ageing populations and rising numbers of concomitant cardiovascular risk factors are contributing to the increasing prevalence of atrial fibrillation (AF) and other chronic diseases.[1 2] A Swedish registry study of 272 186 patients with incident AF reported that 69.5% of patients had at least one of seven other long-term comorbid conditions compared with 29.2% in matched controls.[3] A UK Biobank study of 3651 patients aged 40–70 years with self-reported AF also found the presence of at least one other self-reported long-term comorbidity in 80.4% of participants, compared with 65.3% of 498 986 controls.[4]

Pharmacotherapy is a cornerstone in the management for AF and many of the comorbidities common in patients with AF, such as hypertension, heart failure, coronary artery disease and diabetes. Disease-specific treatment guidelines recommend the prescribing of medication for many patients, and combination therapy is common in those with moderate to severe disease.[5–10] For patients with multimorbidity, the potential benefit of combining evidence-based therapies needs to be balanced with the

risk of adverse health outcomes. Definitions of polypharmacy have varied in research studies, with the most common being *the use of five or more medications*,[11] although there is evidence suggesting a continuum of risk.[12] The challenge of adjusting for multimorbidity is well recognised.[13] Many studies have focused on adverse outcomes in older patients over 65 years. These harms may include increased mortality,[14–17] adverse drug reactions (ADR) and events,[18 19] falls,[14 17 20 21] increased hospitalisations,[14 15 17 22 23] lower quality of life,[24 25] increased healthcare costs[26] and medication burden on patients and carers.[27]

Comparatively little research has been done on the prevalence of polypharmacy in patients with AF and possible associated adverse health outcomes. Polypharmacy prevalence in AF has ranged from 40% to 95% depending on the setting, study population, ascertainment criteria and methods.[28 29] Some medications commonly used by patients with AF, including antihypertensive agents and anticoagulation agents, are leading causes of adverse drug events in the elderly.[19] Many patients also take non-prescription or alternative medicines which carry their own potential for harm and interaction with prescribed medicines.[30] In a cross-sectional study of chronic disease clusters in elderly hospitalised patients, AF with comorbid heart failure showed the third strongest association with polypharmacy.[31] Post hoc analyses of two direct acting oral anticoagulant trials suggest that polypharmacy may be independently associated with adverse health outcomes.[32 33]

As polypharmacy in AF may be an underappreciated risk factor for harm irrespective of anticoagulation status, we performed a systematic review and meta-analysis to summarise the best available evidence.

METHODS

Literature search

This systematic review was registered with PROSPERO and was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[34] PubMed and Embase databases were independently searched by two authors (CG and KNH) without date restriction until 31 July 2019. Keywords used included 'atrial fibrillation', 'polypharmacy', 'polypharmacology', 'pharmacoepidemiology', 'cardiovascular outcomes', 'health outcomes', 'cerebrovascular accident', 'bleeding', 'mortality', 'death', 'hospitalisation', 'hospital admission', 'quality of life', 'transient ischaemic attack' and 'falls'. See online supplementary eTable 1 for an outline of the full search strategy.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they were prospective randomised controlled trials or of observational design, had a minimum follow-up of 3 months and were published in English. Outcomes eligible for inclusion included all-cause or cardiovascular mortality, all-cause or cardiovascular hospitalisations, stroke and systemic embolism, transient ischaemic attack, major bleeding (according to the International Society of Thrombosis and Haemostasis definition as bleeding associated with: reduction in haemoglobin of 20 g/L over a 24-hour period, transfusion of two or more units of red cells, fatal bleeding or bleeding at a critical site; eg, retroperitoneal, pericardial),[35] non-major bleeding, intracranial bleeding, quality of life and falls. These outcomes were selected as they are either commonly studied in the AF population, or of significant clinical importance. Studies were excluded if they were of retrospective design, were not published in English or examined other health outcomes, economic costs or outcomes which were not directly health related, including drug interactions without clinical sequelae.

Study selection and data extraction

Two study investigators (CG and KNH) independently reviewed all articles retrieved by the electronic search to determine eligible studies. Any discrepancies were discussed and resolved by consensus decision. Data extracted from relevant studies included: first author, year of publication, total number of participants, gender of included participants, mean age, follow-up period, AF ascertainment, polypharmacy definition, types of medicines collected from participants, endpoint adjudication and covariates adjusted for. The risk of bias in each of the included studies was assessed using the Quality in Prognosis Studies tool,[36] and subjectively characterised as low, moderate or high.

Statistical analysis

The risk estimate for each outcome was independently extracted by two study investigators (CG and KNH) according to two levels of polypharmacy (moderate and severe). The most adjusted model in each study was used. Heterogeneity across studies was assessed using the I^2 statistic. Publication bias was assessed by visual inspection of funnel plots of effect size against standard error. A two-tailed p value <0.05 was considered statistically significant. All analyses were performed using a random effects model in Review Manager (RevMan) V.5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collection, 2014.

Patient and public involvement

Due to the nature of this research it was undertaken without patient or public involvement. Patients were not invited to comment on the study design or patient-relevant outcomes or to assist with interpretation of the results. Patients did not contribute to the writing or editing of this document for readability or accuracy.

RESULTS

A total of 791 articles were identified from the electronic search, with 65 retrieved for full-text review. Of these, 59 did not meet the inclusion criteria, with the remaining six studies eligible (figure 1). This includes

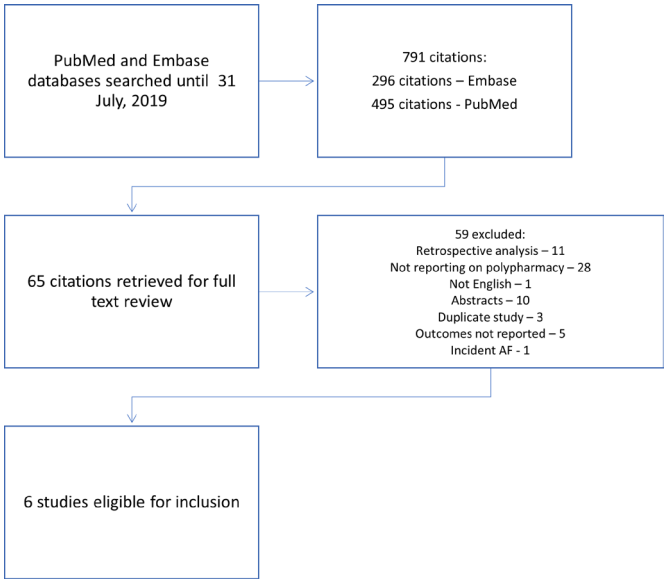

Figure 1 Flow chart of study. AF, atrial fibrillation.

one study examining the impact of polypharmacy on clinical outcomes in an anticoagulated population in which 73% of the study population had AF.[37] The authors of this study were contacted and provided outcomes specific to the AF subpopulation of this study. The prevalence of polypharmacy ranged from 40.1% (≥5 cardiovascular medicines) to 78.8% (≥5 overall medicines).[28 37] More than one of the included studies reported on common outcomes including all-cause mortality, stroke or systemic embolism, major bleeding, intracranial bleeding and clinically relevant non-major bleeding and were able to be used for a meta-analysis,[32 33 37] with the three remaining studies examining other outcomes including cardiovascular mortality[28] and quality of life.[38 39] Due to heterogeneous reporting of quality of life, a meta-analysis of this outcome was unable to be performed. See table 1 for characteristics of the included studies. The total study population of the meta-analysis was 33 602 individuals of which 37.2% were female. In the three studies included in the meta-analysis, risk of bias was assessed as low in two studies,[33 37] and moderate in the other (online supplementary eTable 2).[32]

Polypharmacy definition

There was slight variation in the definition of polypharmacy used across the three studies included in the meta-analysis. For the purpose of this study we have classified moderate polypharmacy as the group of five to nine medications in one study,[33] six to eight in the second study[32] and five to eight in the third study.[37] Severe polypharmacy was classified as ≥10 in one study and ≥9 medicines in two studies. The reference group was zero to four medicines in two studies[33 37] and zero to five medicines in

Table 1 Characteristics of studies included in the meta-analysis

Study	Year of publication	Participants, n	Median age	% female	Reported medication categories	Median duration follow-up (years)	Outcome measures	Covariates adjusted for
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET- AF)[33]	2016	14 264	73	39.7	Reference group: 0–4, 5–9, ≥10 medicines	1.9	All-cause mortality, stroke, non-CNS embolism, vascular death, MI, intracranial bleeding, major bleeding, non-major clinically relevant bleeding	Age, sex, BMI, region, DM, previous stroke/TIA, vascular disease, CHF, hypertension, COPD, PAF, DBP, creatinine clearance (Cockcroft-Gault), heart rate, alcohol use and randomised treatment*
Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE)[32]	2016	18 201	70	35.3	Reference group: 0–5, 6–8, ≥9 medicines	1.8	Stroke, systemic embolism, all-cause mortality, major bleeding, intracranial bleeding, GI bleeding, clinically relevant non-major bleeding	Age, sex, country
Evaluation of Oral Anticoagulation with Vitamin K Antagnoists - the thrombEVAL Study Programme (thrombEVAL)[37]	2019	1137	74	36.8	Reference group: 0–4, 5–8, ≥9 medicines	2.3	All-cause mortality, hospitalisation, stroke, TIA, major bleeding, clinically relevant non-major bleeding, intracranial bleeding	Age, sex, diabetes, dyslipidaemia, hypertension, obesity, family history of MI, current smoking and Charlson Comorbidity Index

*Safety endpoints adjusted for age, sex, region, previous stroke/TIA, anaemia, previous GI bleed, COPD, DBP, creatinine clearance (Cockroft-Gault), platelets, albumin, previous aspirin, vitamin K antagonist, thienopyridine and randomised treatment.
BMI, body mass index; CHF, congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DM, diabetes mellitus; GI, gastrointestinal; MI, myocardial infarction; PAF, paroxysmal atrial fibrillation; TIA, transient ischaemic attack.

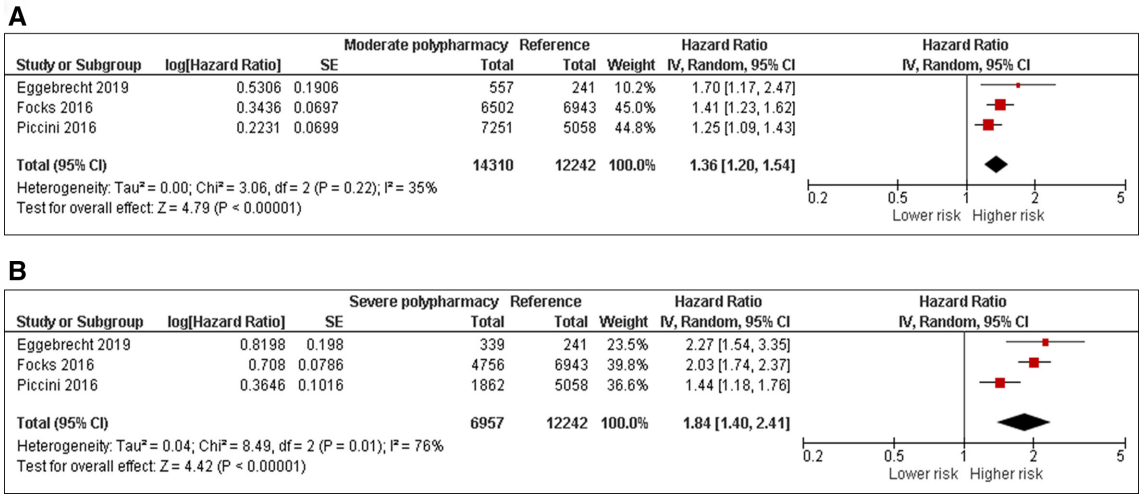

Figure 2 Impact of moderate (A) and severe (B) polypharmacy on all-cause mortality.

the other.[32] See table 1 for an outline of studies eligible for inclusion.

All-cause mortality

Both moderate and severe polypharmacy was associated with significant increases in all-cause mortality (HR 1.36, 95% CI 1.20 to 1.54, p<0.001; HR 1.84, 95% CI 1.40 to 2.41, p<0.001, respectively; see figure 2). There was no evidence of statistical heterogeneity with moderate polypharmacy (I^2=35%, p=0.22), however, there was evidence of heterogeneity with severe polypharmacy (I^2=76%, p=0.01).

Stroke or systemic embolism

Neither moderate nor severe polypharmacy was associated with stroke or systemic embolism (HR 1.09, 95% CI 0.83 to 1.43, p=0.56; HR 1.17, 95% CI 0.79 to 1.74, p=0.44, respectively; figure 3). Moderate polypharmacy did not demonstrate any evidence of statistical heterogeneity with this outcome (I^2=61%, p=0.08), with heterogeneity evident at the severe polypharmacy level (I^2=66%, p=0.05).

Major bleeding

Major bleeding was significantly increased with both moderate and severe polypharmacy (HR 1.32, 95% CI 1.14 to 1.52, p<0.001; HR 1.68, 95% CI 1.35 to 2.09, p<0.001, respectively; figure 4). There was no evidence of statistical heterogeneity with either moderate or severe polypharmacy (I^2=21%, p=0.28; I^2=47%, p=0.15, respectively).

Intracranial bleeding

There was no impact of moderate or severe polypharmacy on intracranial bleeding (HR 1.37, 95% CI 0.85 to 2.19, p=0.19; HR 1.37, 95% CI 0.96 to 1.96, p=0.08, respectively; see figure 5). There was no evidence of statistical heterogeneity at the moderate polypharmacy level (I^2=53%, p=0.12), nor severe polypharmacy with this outcome (I^2=12%, p=0.32).

Clinically relevant non-major bleeding

Both moderate and severe polypharmacy was associated with an increased risk of clinically relevant non-major

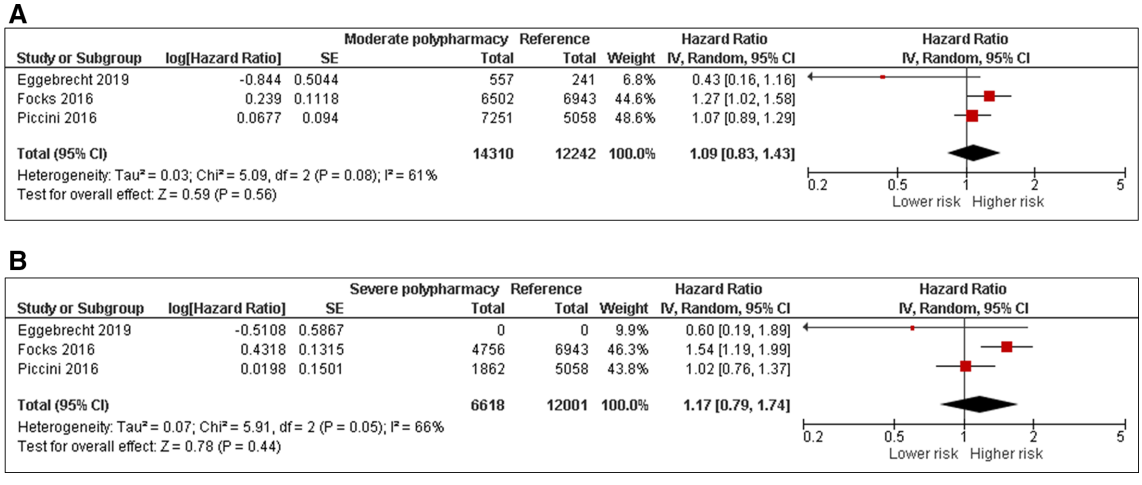

Figure 3 Impact of moderate (A) and severe (B) polypharmacy on stroke or systemic embolism.

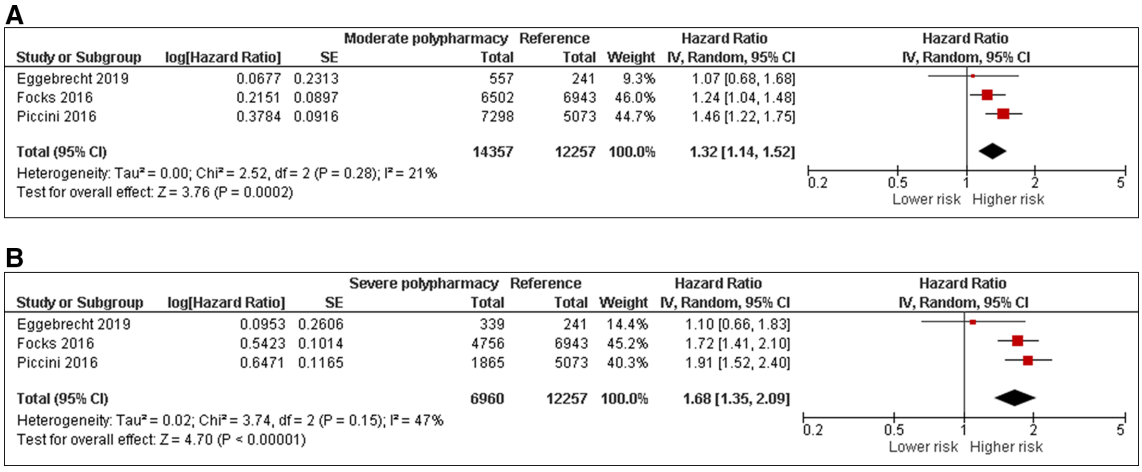

Figure 4 Impact of moderate (A) and severe (B) polypharmacy on major bleeding.

bleeding based on two studies reporting on this outcome (HR 1.12, 95% CI 1.03 to 1.22, p=0.009; HR 1.48, 95% CI 1.33 to 1.64, p<0.001, respectively; see figure 6). Neither moderate nor severe polypharmacy demonstrated any evidence of statistical heterogeneity for this outcome (I^2=0%, p=0.49; I^2=0%, p=0.39, respectively).

Cardiovascular death

Post hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management study, which examined the impact of polypharmacy of cardiovascular medicines only (defined as >5 medicines), demonstrated an increase in the risk of cardiovascular death (unadjusted HR 1.47, 95% CI 1.18 to 1.82, p<0.001) and stroke (unadjusted HR 1.17, 95% CI 0.85 to 1.60, p=0.34).[28] The adjusted relative risk for cardiovascular death was 1.30 (95% CI 1.03 to 1.64, p=0.03).

Hospitalisation

One study examined the impact of polypharmacy on all-cause hospitalisations. In this study of 1137 participants with AF from the Evaluation of Oral Anticoagulation with Vitamin K Antagonists - the thrombEVAL study programme (thrombEVAL) cohort, which assessed outcomes in individuals taking anticoagulant therapy, an adjusted increased risk was observed with both moderate (HR 1.23, 95% CI 1.00 to 1.51; p=0.051) and severe (HR 1.32; 95% CI 1.05 to 1.68; p=0.02) polypharmacy.[37 40]

Quality of life

Two studies examined the impact of polypharmacy on quality of life. Post hoc analysis of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, which examined quality of life in 1762 elderly individuals (>75 years) with AF, demonstrated that >7 medicines were associated with a significant reduction in quality of life as assessed by the EuroQol-5 Dimension (parameter estimate −0.06, p=0.03).[38] There was no impact at other polypharmacy levels (1-3 or 4-6 medicines). Both moderate and severe polypharmacy was associated with a significant reduction in the physical component summary score of the 12-Item Short Form Health Survey (SF-12) (p=0.03 and p<0.0001, respectively), but not the mental component summary score. Similarly, in another study of 662 community-dwelling adults (>65 years) with AF, an unadjusted incremental decline in physical function assessed by self-reported ability to undertake five activities

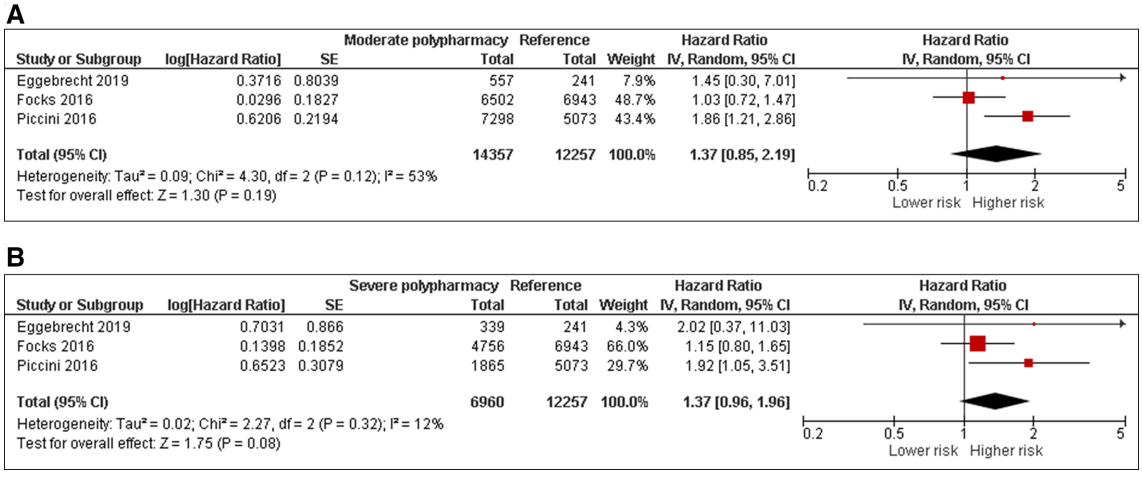

Figure 5 Impact of (A) moderate and (B) severe polypharmacy on intracranial bleeding.

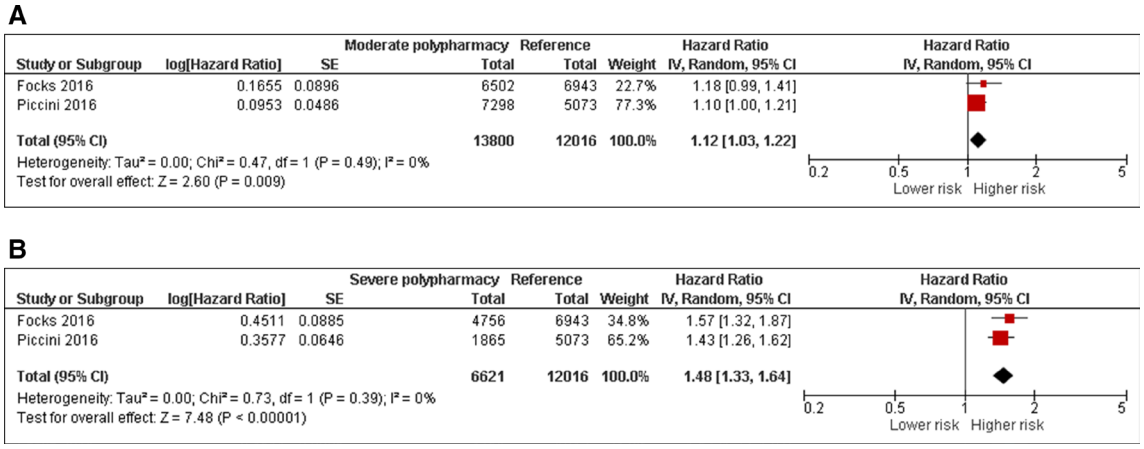

Figure 6 Impact of moderate (A) and severe (B) polypharmacy on clinically relevant non-major bleeding.

was observed with both low (<7 medications) and high (≥7 medications) polypharmacy, respectively.[39]

DISCUSSION

Our systematic review and meta-analysis demonstrates the following in the AF population:

1. Moderate and severe polypharmacy is associated with a 36% and 84% increase in all-cause mortality, respectively.
2. The risk of major bleeding is increased by 32% and 68% for moderate and severe polypharmacy, respectively.
3. Clinically relevant non-major bleeding increased by 12% and 48%, respectively, with moderate and severe polypharmacy.
4. No association was found between any level of polypharmacy and stroke or systemic embolism, or intracranial bleeding.
5. Polypharmacy is associated with an increased risk of cardiovascular death, hospitalisation, reduced quality of life and poorer physical functioning.

To date, there has been a paucity of studies examining the impact of polypharmacy on health outcomes in patients with AF, and few have used outcome data from prospective studies with independent endpoint adjudication as in the present meta-analysis. Given the increasing prevalence of concomitant risk factors in patients with AF,[1 3] it is likely that, similar to other chronic diseases, the use of multiple medicines is driven by comorbid conditions.[41 42] Adjustment for comorbidities is a challenge in polypharmacy research and although the studies in our meta-analysis varied in this regard, two of the three included studies adjusted for common confounding factors with significant HRs found in all outcomes with the exception of stroke or systemic embolism and intracranial bleeding.

The *mechanisms* underlying the adverse outcomes associated with polypharmacy are likely to be multifactorial and may vary between outcomes. Although polypharmacy is a marker for multimorbidity which contributes to poorer outcomes, potentially causal mechanisms that polypharmacy adds could include (1) reduced adherence and persistence to prescribed regimens; (2) drug–drug and drug–disease interactions; and (3) ADRs.

Adherence and persistence to prescribed regimens has been inversely correlated with number of medicines used.[43] In the heart failure population the number of drug-related negative outcomes, including inadequately treated health issues, inadequate doses or duration of treatment and non-adherence, has demonstrated a significant correlation with increasing number of medicines prescribed.[44] In one of the studies included in our meta-analysis 42.4% of patients taking ≥10 medications discontinued their anticoagulant, compared with 35.4% taking 5–9 medications and 31.8% taking 0–4 medications.[33] Polypharmacy may similarly have affected persistence with other medications. Non-adherence to dabigatran in patients with AF, defined as less than 20% adherence, has been shown to be associated with an increase in all-cause mortality and stroke in an observational registry (HR 1.54; 95% CI 1.20 to 1.97; p<0.01).[45]

Drug–drug and drug–disease interactions may be a contributing factor to polypharmacy-associated harm. It is possible that the observed increase in bleeding risk may reflect an increased likelihood of combining certain high-risk medications with anticoagulants.[46] Many commonly used agents have potential interactions with anticoagulants including non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents or others with antiplatelet effects including selective serotonin reuptake inhibitors. Post hoc analyses of the Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY) studydemonstrated that use of NSAIDs was associated with an increased risk of major bleeding, stroke or systemic embolism and all-cause hospitalisations.[47] In the Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) post hoc analysis, aspirin, NSAIDs or prednisone was used by 13.8% in those taking 0–5 medications, 31.7% taking 6–8 and 49.7% taking ≥9 medications. The risk of drug–drug interactions increases with growing numbers of medicines prescribed, with the risk identified to be as high as 82% in individuals prescribed seven or more

medicines.[48] Many of these interactions may be under-recognised by clinicians and possibly result in further use of medicines to treat ADRs. Compounding this situation, current guidelines are often single disease focused, with little advice for clinicians concerning management of the comorbid individual, and the potential for interactions with drug therapy for other conditions.[49] The use of over-the-counter medicines is also under-recognised, with the risk of potentially unknown adverse interactions. A study of 250 individuals attending an anticoagulation clinic in Denmark demonstrated that almost 50% of individuals were taking alternative medicines including fish oil, and some with potential for interactions with warfarin.[50] More research is needed to investigate whether adverse bleeding outcomes in patients with AF using polypharmacy are associated with certain drug–disease interactions or combinations of pharmacotherapy.

ADRs are associated with significant morbidity and mortality and in older patients (>65 years of age) may account for 1 in 10 hospitalisations.[19] As more medicines are taken the risk of ADRs increases. Anticoagulants and cardiovascular agents, commonly used in the AF population, are associated with bleeding and falls which may contribute to increased all-cause mortality either as a direct effect or secondary to discontinuation of therapy.

Our systematic review identified two studies in community-dwelling older adults examining the impact of polypharmacy on quality of life. A secondary analysis of the BAFTA study demonstrated that gender, number of prescribed medications and disability were all independently associated with quality of life. Poorer quality of life was observed in individuals taking greater than three medications, with greater impairment demonstrated in those taking more than seven medications.[38] The other study identified in our systematic review also describes poorer physical functioning, based on an individual's ability to undertake five predetermined activities, with incremental declines observed for moderate and severe polypharmacy.[39] This is consistent with Australian data which demonstrated an incremental association between poorer physical functioning, as determined by the SF-36, with moderate and severe polypharmacy, respectively.[29] Together, these studies provide a strong signal of the association between poorer physical functioning and polypharmacy.

One study from our systematic review described an association between polypharmacy and all-cause hospitalisations. A longitudinal study has shown an increase in age, multimorbidity and polypharmacy in patients with heart failure over the years 1998–2008.[42] The question of whether a similar trend may be contributing to observed increases in AF hospitalisations deserves further investigation.[51 52] Our systematic review did not identify any prospective studies examining the relationship between polypharmacy and falls in the AF population. Many studies in older patient populations have found polypharmacy to be associated with falls, and an unadjusted association was found in a small retrospective study of patients with AF with a mean age of 82 years (p=0.027).[53] Other data have demonstrated an independent association between AF and hip fracture,[54] and raise the possibility that polypharmacy may be a contributing factor to this observation. In the ARISTOTLE study, 8.8% of patients with severe polypharmacy had a history of falls during the year prior to enrolment, compared with 2.3% in those taking zero to five medications (p<0.001).[32] A separate post hoc analysis of the ARISTOTLE study found that patients with a history of falls had an increased adjusted risk of major bleeding and all-cause mortality, and a more than threefold increased risk of falling during the trial.[55] Larger prospective studies are needed to determine the mechanisms contributing to falls in patients with AF and the possible role of polypharmacy-associated decline in physical function.

Deprescribing has been defined as 'the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes'.[56] We are, however, unaware of any studies reporting on deprescribing outcomes specific to patients with AF. Current AF treatment guidelines recommend avoidance of certain medications depending on the clinical context, for example, antiarrhythmic drugs for rate control in those with permanent AF and aspirin monotherapy for stroke prevention.[8] Evidence also suggests that deprescribing of NSAIDs may improve outcomes in anticoagulated patients with AF.[47] The adoption of these and other evidence-based recommendations into practice may be improved by guidelines including a separate discussion and summary of deprescribing advice. Recommendations for managing the overall pharmacotherapy of patients with AF in the context of potential drug interactions and other common comorbidities including hypertension, heart failure and diabetes may also help minimise adverse outcomes.[57 58]

Intervention studies of comprehensive medication review and deprescription of inappropriate pharmacotherapy using shared decision-making are needed to evaluate whether polypharmacy is a modifiable risk factor in patients with AF or represents a risk marker for adverse outcomes.

Limitations

Our study has several limitations worthy of consideration. While two of the included studies in our meta-analysis adjusted for multiple confounders,[33 37] the other had limited adjustment for age, sex and geographical location.[32] Even extensive adjustment however may not account for all variables which influence prescribing and health outcomes, including frailty, falls history and other unmeasured health variables. However, it is possible that polypharmacy represents a 'risk marker' in individuals with highly prevalent comorbidities and is not in itself responsible for the adverse effects observed. Despite heterogeneity in adjustment, the magnitude of effect of polypharmacy on statistically significant outcomes was similar, lending strength to the conclusion of

polypharmacy-associated harm. Furthermore, the associated risk demonstrated a dose-dependent increase, with more 'severe' levels of polypharmacy resulting in incrementally greater risk of adverse events. We were, however, unable to determine the appropriateness of the medicines prescribed for each patient which may also be a contributing factor to polypharmacy-related harm. Other unreported factors may also impact on adverse outcomes, including the number of prescribers caring for individuals. This has been shown to be an independent predictor of adverse drug events,[18 59] with each additional specialist conferring a 19% increase in risk in a multicentre observational study.[18]

Studies included in our meta-analysis are based on polypharmacy at the time of study enrolment, and the duration of polypharmacy during the study is uncertain. Finally, although only three studies were available for meta-analysis, the total number of patients was 33 602 with independently adjudicated outcomes, which strengthens the evidence for polypharmacy-associated harm. Our systematic review identified six studies examining this area, which demonstrates the need for future research to further confirm our findings, in addition to interventions designed to reduce the risk of polypharmacy-related adverse events in AF.

CONCLUSIONS

The growing burden of AF has led to a pressing need to identify ways in which outcomes can be improved in this population. Polypharmacy is common among individuals with AF, and our results demonstrate that it is associated with numerous adverse outcomes. Causal mechanisms underlying this risk are unclear and may be multifactorial, including the use of concomitant high-risk medications, poor adherence or persistence to prescribed regimens, or unclear communication between numerous prescribers, and between prescribers and their patients. Further studies examining deprescription of inappropriate pharmacotherapy in patients with AF are warranted to evaluate whether polypharmacy is a modifiable risk factor.

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Contributors CG and KNH conceived and designed the study. CG and KNH undertook data collection and statistical analysis. CG, KNH, PS, DR and JMH drafted the manuscript. All authors critically revised the manuscript for important content. All authors had access to all data and contributed to the analysis and interpretation of the data.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Correction notice This paper has been updated since first published to correct author name 'Prashanthan Sanders'.

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